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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,046	XU ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/27/04, 4/30/04 & 11/8/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12,26-35,38-50,53-61 and 63-72* is/are pending in the application.

4a) Of the above claim(s) *26-35,38-50,53-61,63-68 and 70-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12 and 69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/22/01* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/22/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed 8/27/04 and Applicant's responses filed 4/30/04 and 11/8/04 are acknowledged and have been entered.

2. Applicant's election with traverse of Group II (claims 1-12 and newly added claim 69), and species of immunoliposome comprising a pre-linked antibody fragment that binds a transferrin receptor and further comprises DNA encoding wild type p53 in Applicant's said responses filed 8/27/04 and 4/30/04 are acknowledged.

The basis for the traversal is of record in Applicant's said responses filed 8/27/04 and 4/30/04, briefly, (1) that Applicant wishes the Examiner to broaden the species election to an immunoliposome comprising a pre-linked antibody fragment that binds a transferring receptor and further comprises a gene, in light of liposomes being useful gene delivery tools, and plasmid DNA carrying any of a wide variety of genes can be used in the immunoliposome; and (2) that the claims have been amended and are now not taught by the Compagnon et al reference applied in the Election/Restriction requirement mailed 1/2/04 and thus have unity of invention.

Applicant's arguments have been fully considered but are not persuasive.

It is the Examiner's position that (1) Applicant is reminded if the elected species is free of the art, the search will be extended to include another species; and (2) at the time the Election/Restriction requirement was mailed, the claims lacked unity of invention in light of the Compagnon et al reference as enunciated in the said requirement mailed 1/2/04 at item #3.

The requirement is still deemed proper and is therefore made FINAL.

Newly added claims 70-72 are drawn to the inventions of Groups IV, V and VII, respectively.

Accordingly, claims 26-35, 38-50, 53-61, 63-68 and newly added claims 70-72 (non-elected groups I and III-X) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-9, 12 and 69 are currently being examined.

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 (e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or

continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

4. The drawings are objected to because Figure 9 contains handwritten text. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the Examiner, the Applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 8 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 8 is indefinite in the recitation of "DOPE" and "MPB" because it is not clear what is meant. It is suggested that Applicant amend the said claims to recite the names for the indicated acronyms.

8. For the purpose of prior art rejections, the filing date of the instant claims 1-12 and 69 is deemed to be the filing date of PCT US00/04392, i.e. 2/22/00, as the parent provisional application 60/121,133 does not support the claimed limitations of the instant application. The limitations of the ratios recited at the last 3 lines of claim 1, "MPB" in claim 8 and "antibody fragment is a single chain" in claim 9 are not disclosed in 60/121,133. With regard to the latter, 60/121,133 only discloses scFv, single chain Fv fragment.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

10. Claims 1, 3-9 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by MacLean et al (Int. J. Oncol. 11: 325-352, 1997) as evidenced by Martin et al (J. Biol. Chem. 267(1): 286-288, 1982), by Laukkanen et al (Biochemistry 33: 11664-11670, 1994) and by Gershon et al (Biochemistry 32: 7143-7151, 1993) and by Lesoon-Wood et al (Human Gene Therapy 6: 395-405, 1995).

MacLean et al teach cationic immunoliposomes comprising DNA wherein the said immunoliposomes are targeted by the conjugated antibody/fragment thereof to a tumor cell. MacLean et al teach that the antibody/fragment thereof can comprise a lipid tag, and that it can be covalently bound to the lipsome via a sulfur atom that was part of a sulfhydryl group on the antibody/fragment thereof, in the case of Fab' antibody fragments, the reactive thiol group is in the hinge region, i.e., at the carboxy terminus of the said fragments. MacLean et al teach pharmaceutical compositions comprising the nucleic-acid cationic immunoliposomes and their use in treating cancer. MacLean et al teach cationic liposomes containing wild type p53 DNA and their use in tumor size reduction and prevention of metastases. MacLean et al teach use of antibodies coupled to liposomes to target the liposomes to cell types such as leukemic cells, solid tumor cells, lung endothelial cells and nerve cells in vivo. MacLean et al teach that succinimyl-maleimide crosslinkers are used to attach antibodies/fragments thereof to liposomes and that Martin et al teach use of these said crosslinkers to attach Fab' to liposomes. Laukkanen et al teach attachment of a scFv mAb comprising a lipid tag to liposomes. MacLean et al teach that Gershon et al teach different ratios of DNA to liposome in ug of liposome to concentration of DNA and that the resulting immunoliposomes comprising nucleic acid are highly efficient delivery vehicles for the said DNA. MacLean et al teach that Lesoon-Wood teach a lipid/DNA ratio of 11.4 nmol/1 ug.

Evidentiary reference Martin et al teach coupling of Fab'fragments at 0.5-4.0 mg/ml to 1-2 umol of lipid, and yields of up to 3000 Fab' molecules/vescicle.

Evidentiary reference Laukkanen et al teach attachment of a scFv mAb comprising a lipid tag to liposomes and that the yield is about 2000 antibody molecules per liposome. Evidentiary reference Laukkanen et al teach use of other antibody fragments such as Fab and Fv. Evidentiary reference Gershon et al teach that complexes formed between cationic liposomes and nucleic acid molecules represent highly efficient vehicles for delivery of DNA and RNA

into a large variety of eukaryotic cells, that charge ratio of nucleic acid to immunoliposome is independent of DNA size in the range of 100-23,000 base pairs. Gershon et al teach different ratios of DNA to liposome in ug of liposome to concentration of DNA.

Evidentiary reference Lesoon-Wood et teach a DNA/lipid ratio of 1ug DNA to 11.4 nmol lipid, which is in the range recited in instant claim 1, in a liposome comprising DNA encoding wild type p53.

Although neither MacLean et al, nor Martin et al, nor Laukkanen et al teach the ratio of protein:lipid recited in instant claim 1, Martin et al teaches a ratio in concentration protein: umol lipid and resulting yields, and Laukkanen et al teach the yield resulting from their process of preparing immunoliposomes is close to that taught by Martin et al. Although neither MacLean et al nor Martin et al, nor Laukkanen et al teach the nucleic acid:lipid ratio recited in instant claim 1, Gershon et al teach different ratios of DNA to liposome in ug of liposome to concentration of DNA, and Lesson-Wood et al teach a DNA/lipid ratio recited in instant claim 1. Therefore, the claimed nucleic-acid immunoliposome complex appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

With regard to the recitation of the ratio of protein:lipid in base claim 1, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps...(and) patentability is based on the product itself. See MPEP 2113.

11. Claims 1, 3-8 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,071,533.

U.S. Patent No. 6,071,533 discloses nucleic acid-cationic immunoliposome complexes and pharmaceutical compositions thereof, the said complexes comprising cationic liposomes that have been coupled with antibodies or fragments thereof that target the liposomes to a specific cell type such as a cancer cell, and further comprising a nucleic acid molecule such as DNA encoding p53 that is to be delivered to the said specific cell type. U.S. Patent No. 6,071,533 discloses that targeted molecules include growth factor receptors. U.S. Patent No. 6,071,533 discloses that the targeting moiety may be directly conjugated to the liposome by means well known in the art, and that the antibody may be reacted with a derivatized lipid, i.e., a lipid tag, and conjugated through a thioether linkage, i.e., the antibody is covalently bound to DOPE in the liposome linked to a sulfhydryl reacting group. U.S. Patent No. 6,071,533 discloses that 1 ug DNA is mixed with 5-15 nmol lipid (especially abstract, column 2 at lines 22-25 and 61-67, column 3, column 5, column 6, column 8 at lines 1-3, column 8 at lines 65-67, column 9 at

lines 1-20, column 12 at section "E", column 13, column 14, column 15 at lines 1-19, column 16 at section "III", column 18 at lines 29-54).

Although U.S. Patent No. 6,071,533 does not disclose the ratio of protein:lipid recited in claim 1, the claimed nucleic-acid immunoliposome complex appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. The claimed nucleic-acid immunoliposome complex appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

With regard to the recitation of the ratio of protein:lipid in base claim 1, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps...(and) patentability is based on the product itself. See MPEP 2113.

12. Claims 1, 3-9 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,210,707 B1.

U.S. Patent No. 6,210,707 B1 discloses nucleic acid-cationic immunoliposome complexes and pharmaceutical compositions thereof, the said complexes comprising cationic liposomes that have been coupled with antibodies or fragments thereof that target the liposomes to a specific cell type such as a cancer cell, and further comprising a nucleic acid molecule such as DNA that is to be delivered to the said specific cell type. U.S. Patent No. 6,210,707 B1 discloses that targeted molecules include growth factor receptors. U.S. Patent No. 6,210,707 B1 discloses that the targeting moiety, including antibodies and fragments thereof such as scFv, may be directly conjugated to the liposome by means well known in the art, including covalently, and that the antibody may be reacted with a derivatized lipid, i.e., a lipid tag, and conjugated through a thioether linkage, i.e., the antibody is covalently bound to DOPE in the liposome linked to a sulfhydryl reacting group. U.S. Patent No. 6,210,707 B1 discloses that 1 ug DNA is mixed with 5-15 nmol lipid, and that 100 ug Fab' mAb fragments were reacted with 2umol lipid or 15.6 ug of scFv mAb fragments were reacted with 1 umol of lipid (especially abstract, column 3 at lines 30-49, column 4, column 5, column 6, column 7 at lines 4-44, column 8 at lines 42-52, column 11, column 12 at lines 33-59, column 13, column 14, column 15 at lines 1-19, column 16, column 18 at section "E", column 20 at lines 29-32, column 32, column 33, column 36 at lines 24-60).

Although U.S. Patent No. 6,210,707 B1 does not disclose the ratio of protein:lipid recited in claim 1 (w:w ratio), U.S. Patent No. 6,210,707 B1 discloses the ratio in ug protein: umol lipid. The claimed nucleic-acid immunoliposome complex appears to be the same or similar to

the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

With regard to the recitation of the ratio of protein:lipid in base claim 1, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps...(and) patentability is based on the product itself. See MPEP 2113.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-8, 12 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al (Human Gene Therapy: 467-475, 3/1/1997, IDS reference) in view of U.S. Patent No. 6,200,956 B1 and MacLean et al (Int. J. Oncol. 11:325-352, 1997).

Xu et al teach transferrin-cationic liposomes mixed with DNA encoding wild type p53, with the optimal DNA/liposome/Tf protein ratio of 1ug DNA/8-10 nmol lipid/10-15 ug protein, i.e., the same ratio recited in instant claim 1 for ratio of DNA/lipid/antibody protein. Xu et al teach use of the nucleic acid transferrin-cationic liposomes are effective for transfection of tumor cells, administration results in significant inhibition of tumor growth and prevents relapse and metastasis of mammary tumors in nude mice, and for treatment of head and neck cancer.

Xu et al do not teach use of a cationic liposome comprising nucleic acid encoding wild type p53 and an antibody/fragment thereof to the transferrin receptor.

U.S. Patent No. 6,200,956 B1 discloses immunoliposomes, including cationic polymers of cationic lipids chemically coupled, covalently or non-covalently, to a ligand of a membrane receptor present at the surface of a target cell type, such as a tumor cell, i.e., is an immunoliposome, and further comprising DNA that is to be delivered to the said target cell type, i.e., is a nucleic acid-cationic immunoliposome complex, and pharmaceutical compositions thereof. Patent No. 6,200,956 B1 further discloses that transferrin and antibodies/fragments of antibodies are ligands of the target cell surface molecule transferrin receptor, i.e., are targeting molecules for cells such as tumor cells (especially column 1 at lines 63-67, column 2 at lines 1-15 and 26-33 and column 4 at lines 20-64).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an antibody or fragment thereof to the transferrin receptor as disclosed by U.S. Patent No. 6,200,956 B1 in place of transferrin in the nucleic acid-cationic liposome taught by Xu et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer as disclosed by both patents.

15. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al (Human Gene Therapy: 467-475, 3/1/1997, IDS reference) in view of U.S. Patent No. 6,200,956 B1 and MacLean et al (Int. J. Oncol. 11:325-352, 1997) as applied to claims 1-8, 12 and 69 above, and further in view of U.S. Patent No. 4,946,778.

Xu et al and U.S. Patent No. 6,200,956 B1 have both been discussed supra, hereafter referred to as "the combined references".

The combined references do not teach wherein the antibody fragment is a single chain.

U.S. Patent No. 4,946,778 discloses that single chain antibody fragments are smaller, more stable and can be produced more inexpensively. U.S. Patent No. 4,946,778 further discloses that use of single chain antibodies increases the safety and efficacy of therapeutic applications (especially column 3 at lines 29-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an antibody or fragment thereof to the transferrin receptor as disclosed by U.S. Patent No. 6,200,956 B1 in place of transferrin in the nucleic acid-cationic liposome taught by Xu et al and to have used the single chain antibody disclosed by U.S. Patent No. 4,946,778.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer with more safety and efficacy as disclosed for use of single chain antibodies in therapeutic applications by U.S. Patent No. 4,946,778.

16. Claims 1-9, 12 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacLean et al (Int. J. Oncol. 11: 325-352, 1997), Martin et al (J. Biol. Chem. 267(1): 286-288, 1982), Laukkanen et al (Biochemistry 33: 11664-11670, 1994), Gershon et al (Biochemistry 32: 7143-7151, 1993) and Leeson-Wood et al (Human Gene Therapy 6:395-405, 1995) in view of U.S. Patent No. 6,200,956 B1.

MacLean et al teach cationic immunoliposomes comprising DNA wherein the said immunoliposomes are targeted by the conjugated antibody/fragment thereof to a tumor cell. MacLean et al teach that the antibody/fragment thereof can comprise a lipid tag, and that it can be covalently bound to the lipsome via a sulfur atom that was part of a sulfhydryl group on the antibody/fragment thereof, in the case of Fab' antibody fragments, the reactive thiol group is in the hinge region, i.e., at the carboxy terminus of the said fragments. MacLean et al teach pharmaceutical compositions comprising the nucleic-acid cationic immunoliposomes and their use in treating cancer. MacLean et al teach cationic liposomes containing wild type p53 DNA and their use in tumor size reduction and prevention of metastases. MacLean et al teach use of antibodies coupled to liposomes to target the liposomes to cell types such as leukemic cells, solid tumor cells, lung endothelial cells and nerve cells in vivo. MacLean et al teach that succinimyl-maleimide crosslinkers are used to attach antibodies/fragments thereof to liposomes and that Martin et al (in the reference cited above) teach use of these said crosslinkers to attach Fab' to liposomes, that Laukkanen et al (in the reference cited above) teach attachment of a scFv mAb comprising a lipid tag to liposomes. MacLean et al teach that Gershon et al (in the reference cited above) teach different ratios of DNA to liposome in ug of liposome to concentration of DNA and that the resulting immunoliposomes comprising nucleic acid are highly efficient delivery vehicles for the said DNA.

MacLean et al do not teach the ratios recited in instant base claim 1, nor that the antibody or antibody fragment is capable of binding to a transferrin receptor.

Martin et al teach coupling of Fab'fragments at 0.5-4.0 mg/ml to 1-2 umol of lipid, and yields of up to 3000 Fab' molecules/vescicle.

Laukkanen et al teach attachment of a scFv mAb comprising a lipid tag to liposomes and that the yield is about 2000 antibody molecules per liposome. Evidentiary reference Laukkanen et al teach use of other antibody fragments such as Fab and Fv.

Gershon et al teach that complexes formed between cationic liposomes and nucleic acid molecules represent highly efficient vehicles for delivery of DNA and RNA into a large variety of eukaryotic cells, that charge ratio of nucleic acid to immunoliposome is independent of DNA size in the range of 100-23,000 base pairs. Gershon et al teach different ratios of DNA to liposome in ug of liposome to concentration of DNA.

Lesoon-Wood et teach a DNA/lipid ratio of 1ug DNA to 11.4 nmol lipid, which is in the range recited in instant claim 1, in a liposome comprising DNA encoding wild type p53.

U.S. Patent No. 6,200,956 B1 discloses immunoliposomes, including cationic polymers of cationic lipids chemically coupled, covalently or non-covalently, to a ligand of a membrane receptor present at the surface of a target cell type, such as a tumor cell, i.e., is an immunoliposome, and further comprising DNA that is to be delivered to the said target cell type, i.e., is a nucleic acid-cationic immunoliposome complex, and pharmaceutical compositions thereof. U.S. Patent No. 6,200,956 B1 discloses that wild type p53 is a tumor suppressor gene. U.S. Patent No. 6,200,956 B1 further discloses that transferrin and antibodies/fragments of antibodies are ligands of the target cell surface molecule transferrin receptor, i.e., are targeting molecules for cells such as tumor cells (especially column 1 at lines 63-67, column 2 at lines 1-15 and 26-33 and column 4 at lines 20-64).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the ratios taught by Martin et al, Laukkanen et al, Gershon et al and Lesoon-Wood et al in the nucleic acid cationic immunoliposome taught by MacLean et al and to have used the antibody/fragment thereof that can bind to transferrin receptor as disclosed by U.S. Patent No. 6,200,956 B1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to target nucleic acid encoding wild type p53 taught by MacLean et al in the cationic immunoliposome taught by MacLean et al, Martin et al, Laukkanen et al, Gershon et al and Lesoon-Wood et al by using the transferring receptor antibody/fragment thereof disclosed by U.S. Patent No. 6,200,956 B1 to target the complex to tumor cells as disclosed by U.S. Patent No. 6,200,956 B1.

Although neither MacLean et al, nor Martin et al, nor Laukkanen et al teach the ratio of protein:lipid recited in instant claim 1, Martin et al teaches a ratio in concentration protein: umol lipid and resulting yields, and Laukkanen et al teach the yield resulting from their process of preparing immunoliposomes is close to that taught by Martin et al. Although neither MacLean et al nor Martin et al, nor Laukkanen et al teach the nucleic acid:lipid ratio recited in instant claim 1, Gershon et al teach different ratios of DNA to liposome in ug of liposome to concentration of DNA, and Lesson-Wood et al teach a DNA/lipid ratio recited in instant claim 1. Therefore, the claimed nucleic-acid immunoliposome complex appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

With regard to the recitation of the ratio of protein:lipid in base claim 1, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps...(and) patentability is based on the product itself. See MPEP 2113.

17. Claims 1-8, 12 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,071,533 in view of U.S. Patent No. 6,200,956 B1.

U.S. Patent No. 6,071,533 discloses nucleic acid-cationic immunoliposome complexes and pharmaceutical compositions thereof, the said complexes comprising cationic liposomes that have been coupled with antibodies or fragments thereof that target the liposomes to a specific cell type such as a cancer cell, and further comprising a nucleic acid molecule such as DNA encoding p53 that is to be delivered to the said specific cell type. U.S. Patent No. 6,071,533 discloses that targeted molecules include growth factor receptors. U.S. Patent No. 6,071,533 discloses that the targeting moiety may be directly conjugated to the liposome by means well known in the art, and that the antibody may be reacted with a derivatized lipid, i.e., a lipid tag, and conjugated through a thioether linkage, i.e., the antibody is covalently bound to DOPE in the liposome linked to a sulfhydryl reacting group. U.S. Patent No. 6,071,533 discloses that 1 ug DNA is mixed with 5-15 nmol lipid (especially abstract, column 2 at lines 22-25 and 61-67, column 3, column 5, column 6, column 8 at lines 1-3, column 8 at lines 65-67, column 9 at lines 1-20, column 12 at section "E", column 13, column 14, column 15 at lines 1-19, column 16 at section "III", column 18 at lines 29-54).

U.S. Patent No. 6,071,533 does not disclose wherein the antibody or fragment thereof is capable of binding to a transferrin receptor.

U.S. Patent No. 6,200,956 B1 discloses immunoliposomes, including cationic polymers of cationic lipids chemically coupled, covalently or non-covalently, to a ligand of a membrane receptor present at the surface of a target cell type, such as a tumor cell, i.e., is an immunoliposome, and further comprising DNA that is to be delivered to the said target cell type, i.e., is a nucleic acid-cationic immunoliposome complex, and pharmaceutical compositions thereof. U.S. Patent No. 6,200,956 B1 discloses that wild type p53 is a tumor suppressor gene. U.S. Patent No. 6,200,956 B1 further discloses that transferrin and antibodies/fragments of antibodies are ligands of the target cell surface molecule transferrin receptor, i.e., are targeting molecules for cells such as tumor cells (especially column 1 at lines 63-67, column 2 at lines 1-15 and 26-33 and column 4 at lines 20-64).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the antibody to transferrin disclosed by U.S. Patent No. 6,200,956 B1 in the invention of U.S. Patent No. 6,071,533.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to target tumor cells with nucleic acid encoding wild type p53/ cationic immunoliposomes as disclosed by both patents using an antibody or fragment thereof to the transferrin receptor as disclosed by U.S. Patent No. 6,200,956 B1 because both teach targeting to tumor cells using antibodies to cell surface receptors on tumor cells.

Although U.S. Patent No. 6,071,533 does not disclose the ratio of protein:lipid recited in claim 1, the claimed nucleic-acid immunoliposome complex appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. The claimed nucleic-acid immunoliposome complex appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

With regard to the recitation of the ratio of protein:lipid in base claim 1, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps...(and) patentability is based on the product itself. See MPEP 2113.

18. Claims 1-9, 12 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,210,707 B1 in view of U.S. Patent No. 6,200,956 B1.

U.S. Patent No. 6,210,707 B1 discloses nucleic acid-cationic immunoliposome complexes and pharmaceutical compositions thereof, the said complexes comprising cationic liposomes that have been coupled with antibodies or fragments thereof that target the liposomes to a specific cell type such as a cancer cell, and further comprising a nucleic acid molecule such as DNA that is to be delivered to the said specific cell type. U.S. Patent No. 6,210,707 B1 discloses that targeted molecules include growth factor receptors. U.S. Patent No. 6,210,707 B1 discloses that the targeting moiety, including antibodies and fragments thereof such as scFv, may be directly conjugated to the liposome by means well known in the art, including covalently, and that the antibody may be reacted with a derivatized lipid, i.e., a lipid tag, and conjugated through a thioether linkage, i.e., the antibody is covalently bound to DOPE in the liposome linked to a sulfhydryl reacting group. U.S. Patent No. 6,210,707 B1 discloses that 1 ug DNA is mixed with 5-15 nmol lipid, and that 100 ug Fab' mAb fragments were reacted with 2umol lipid or 15.6 ug of scFv mAb fragments were reacted with 1 umol of lipid (especially abstract, column 3 at lines 30-49, column 4, column 5, column 6, column 7 at lines 4-44, column 8 at lines 42-52, column 11, column 12 at lines 33-59, column 13, column 14, column 15 at lines 1-19, column 16, column 18 at section "E", column 20 at lines 29-32, column 32, column 33, column 36 at lines 24-60).

U.S. Patent No. 6,210,707 B1 does not disclose wherein the antibody or fragment thereof is capable of binding to a transferrin receptor.

U.S. Patent No. 6,200,956 B1 discloses immunoliposomes, including cationic polymers of cationic lipids chemically coupled, covalently or non-covalently, to a ligand of a membrane receptor present at the surface of a target cell type, such as a tumor cell, i.e., is an immunoliposome, and further comprising DNA that is to be delivered to the said target cell type, i.e., is a nucleic acid-cationic immunoliposome complex, and pharmaceutical compositions thereof. U.S. Patent No. 6,200,956 B1 discloses that wild type p53 is a tumor suppressor gene. U.S. Patent No. 6,200,956 B1 further discloses that transferrin and antibodies/fragments of antibodies are ligands of the target cell surface molecule transferrin receptor, i.e., are targeting molecules for cells such as tumor cells (especially column 1 at lines 63-67, column 2 at lines 1-15 and 26-33 and column 4 at lines 20-64).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the antibody to transferrin disclosed by U.S. Patent No. 6,200,956 B1 in the invention of U.S. Patent No. 6,210,707 B1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to target tumor cells with nucleic acid encoding wild type p53/ cationic immunoliposomes as disclosed by both patents using an antibody or fragment thereof to the transferrin receptor as disclosed by U.S. Patent No. 6,200,956 B1 because both teach targeting to tumor cells using antibodies to cell surface receptors on tumor cells.

Although U.S. Patent No. 6,210,707 B1 does not disclose the ratio of protein:lipid recited in claim 1 (w:w ratio), U.S. Patent No. 6,210,707 B1 discloses the ratio in ug protein: umol lipid. The claimed nucleic-acid immunoliposome complex appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

With regard to the recitation of the ratio of protein:lipid in base claim 1, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps...(and) patentability is based on the product itself. See MPEP 2113.

19. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,071,533 in view of U.S. Patent No. 6,200,956 B1 as applied to claims 1-8, 12 and 69 above, and further in view of U.S. Patent No. 4,946,778.

U.S. Patent No. 6,071,533 and U.S. Patent No. 6,200,956 B1 have been discussed supra, hereafter referred to as "the combined references".

The combined references do not teach wherein the antibody fragment is a single chain.

U.S. Patent No. 4,946,778 discloses that single chain antibody fragments are smaller, more stable and can be produced more inexpensively. U.S. Patent No. 4,946,778 further discloses that use of single chain antibodies increases the safety and efficacy of therapeutic applications (especially column 3 at lines 29-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an antibody or fragment thereof to the transferrin receptor as disclosed by U.S. Patent No. 6,200,956 B1 in place of transferrin in the nucleic acid-cationic liposome taught by the combined references and to have used the single chain antibody disclosed by U.S. Patent No. 4,946,778.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer with more safety and efficacy as disclosed for use of single chain antibodies in therapeutic applications by U.S. Patent No. 4,946,778.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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